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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,994	CHAPARIAN ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *5,6,10-14,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-9,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) ~~Paper No(s).~~ Filed 4/8/03 & 5/23/03
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I in the paper filed 6/30/03 is acknowledged. The traversal is on the ground(s) that all of the groups relate to "cloning and items used for cloning." This is not found persuasive because, as noted in the requirement for restriction, the claims in this 371 application are not joined by a special technical feature as required to establish unity of invention, as the cloning methods recited in the first named invention are anticipated in the prior art. These methods therefore, are not a special technical feature that joins the claimed inventions. Thus, for the reasons of record, the rejection is maintained.

The requirement is still deemed proper and is therefore made FINAL.

Specification

2. The computer readable form submitted has been entered. However, the application is not in compliance with the sequence rules because throughout the specification there are recited sequences that are not properly identified with sequence identifies, see for example page 26 and tables III and IV which each recite a multiplicity of such nucleic acid sequences. Correction is required.

3. The amendment filed 2/18/02 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The statement incorporating the provisional applications by reference is new matter. The original specification filed in a 371 application is the specification

filed for the international application. The addition of an incorporation by reference of the priority documents to this specification is new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 2, 3, 4, 7, 8, 9, 15, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite over the recitation "the targeted genes/cluster" because it is not clear if this recitation is meant to refer to targeted genes and gene clusters, thus requiring the isolation of both a gene and a putative cluster, or if this recitation is meant to refer to cloning targeted genes or gene clusters. The use of the slash between the two words is confusing. Furthermore, the recitation of "the targeted" genes is indefinite because the claim does not previously set forth a specifically targeted gene or cluster. Claims 2-4 depend from claim 1 and are rejected over this same recitation.

Claim 7 is indefinite over the recitation "trimethoprim coding genes" because trimethoprim is not a polypeptide, and thus it is unclear from the language of the claims what exactly is meant by a trimethoprim coding gene, since genes encode polypeptides. Claims 8-9 depend from claim 7 and are rejected over this same recitation.

Claim 9 is indefinite over the recitation "a primer containing a target oligonucleotide coding for DHFR2" because it is not clear if applicant intends that the primer contain the entire

coding sequence of the DHFR2 or if the primer merely be specific for the portion of such a coding sequence.

Claim 15 is indefinite because it is unclear how the recited method steps accomplish the goal set forth in the preamble. That is, it is not clear how isolating and cloning targeted genes/clusters accomplishes the cloning of an entire family of genes. It is not clear if applicant is setting forth that any targeted genes or clusters are equivalent to cloning of an entire family of genes or if the method lacks recitation of the isolation of entire families of genes. Additionally, the preamble recites a method of "degenerate cloning" but does not set forth any steps which appear to relate to degenerate cloning, per se, and thus again it is not clear if applicant is intending to claim any cloning method or degenerate cloning in particular. Claim 16 does not overcome this issue and is also indefinite for this reason.

Claim 15 is further indefinite over the recitation "the targeted genes/cluster" because it is not clear if this recitation is meant to refer to targeted genes and gene clusters, thus requiring the isolation of both a gene and a putative cluster, or if this recitation is meant to refer to cloning targeted genes or gene clusters. The use of the slash between the two words is confusing. Claim 16 does not overcome this issue and is also indefinite for this reason.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 2, 3, 4, 15, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Rovnak *et al.* (Journal of Virology, May 1998, p. 4237-4242).

Rovnak *et al.* teach a method for targeted cloning and enrichment of genes and gene clusters by directly isolating and subsequent cloning the targeted genes/cluster (p. 4338). In particular, Rovnak *et al.* use a degenerate PCR methodology to isolate and clone targeted DNA polymerase genes of the herpesvirus family.

Further, with regard to claim 2, Rovnak *et al.* teach that the isolating step includes the steps of:

creating a primer containing a target oligonucleotide (p. 4238, Col. 1; also Table 1);

adding the primer to a sample of DNA (p. 4238, Col. 1); and

performing PCR to replicate genes targeted by the primer (p. 4238, Col. 1-Col. 2).

With regard to claim 3, Rovnak *et al.* teach that the creating step further includes creating a primer using degenerate PCR, k-tuple, and template derivation. Specifically, Rovnak *et al.* amplify a sequence using degenerate PCR. Rovnak *et al.* then align the sequence with other polymerase sequences of bovine herpesviruses using MegAlign software (DNAStar, Inc.) (p. 4238, Col. 2). The alignment with the MegAlign software inherently uses an algorithm that employs a k-tuple parameter (as was confirmed via a conversation between the examiner and a technical support technician at DNAStar on 9/3/03). Finally, Rovnak *et al.* select primers from the sequences presented in Figure 2A, which sequences are the previously the aligned nucleic acid sequences (p. 4239, Col. 1). This is considered a step of template derivation because the template for the primers is determined using the analysis of the sequence, thus the template is

derived from the sequences recited in the figure. Thus, Rovnak *et al.* have used degenerate PCR, k-tuple, and template derivation to select (i.e. create) primers.

With regard to claim 4, Rovnak *et al.* teach that the performing step includes performing degenerate, nested and temperature gradient PCR. Specifically, primers used by Rovnak *et al.* are degenerate primers (Table 1). Rovnak *et al.* specifically characterize the PCR process they use as a "nested PCR assay," (p. 4238, Col. 2). With regard to the limitation that the PCR be "temperature gradient" this reference teaches temperature gradient PCR insofar as the gradient includes temperatures where hybridization, primer extension, and denaturation reactions all occur at different temperatures (p. 4238, Col. 1).

With regard to claim 15, Rovnak *et al.* teach a method of providing degenerate cloning of an entire family of genes from a mixed DNA sample by directly isolating and subsequent cloning targeted genes/clusters (p. 4338). In particular, Rovnak *et al.* use a degenerate PCR methodology to isolate and clone DNA targeted DNA polymerase genes of the herpesvirus family. The genes cloned using the method of Rovnak *et al.* are considered to be the "entire family" insofar as the family includes of the genes that will be amplified by the degenerate primers used by Rovnak *et al.* from the DNA sample.

With regard to claim 16, Rovnak *et al.* teach that the isolating step includes:

degenerately cloning a target oligonucleotide (see primers used for degenerate cloning via PCR- Table 1);

creating a primer containing the target oligonucleotide (p. 4239, Col. 2);

adding the primer to a mixed sample of DNA (p. 4239, Col. 2); and

performing PCR to replicate the genes targeted by the primer (p. 4239, Col. 2).

Rovnak *et al.* degenerately clone a DAN purified from tumor cells of a BLV-positive, lymphosarcomatous cow (referred to as pBLHV, see methods, p. 4238, Col. 2, and p. 4238, Col. 2). Subsequently, the cloned was excised and sequenced, and aligned with other sequences derived from the bovine lymphoma DNA and known herpesvius agents of cattle, using this alignment to select primers to the target oligonucleotide (p. 4239, Col. 2), followed by seminested PCR amplification to replicate the genes targeted by the primer (p. 4239).

Thus, the teachings provided by Rovnak *et al.* meet all of the limitations of the rejected claims.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 7-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the Invention

The claims are drawn to methods of isolating trimethoprim coding genes by directly isolating and cloning the genes. The claims themselves are unclear, because it is not clear from the claims precisely what is intended by a "trimethoprim coding gene" as trimethoprim itself is not a polypeptide sequence, and is therefore not encoded by a gene. A depiction of the chemical structure of trimethoprim is attached to this office action. An interpretation of the claims also

includes an invention directed towards the isolation of genes that encode enzymes in a putative biosynthetic pathway for the production of trimethoprim. In this case, the nature of the invention involves identifying such genes and then isolating and cloning them.

Scope of the Claims

Claim 7 generically includes any methods which comprise direct isolation and subsequent cloning of the recited trimethoprim coding genes. Claim 8 recites further steps for the isolation step of creating a primer, adding the primer to a sample of DNA, and performing PCR to replicate the trimethoprim coding genes. Claim 9 further still recites that the creating a primer includes creating a primer containing target oligonucleotide coding for DHFR2. Within the scope of the claims is the isolation of any or all genes which would be useful for the synthesis of trimethoprim, these genes being isolated from any or all organisms contain such genes.

State of the Art

Trimethoprim is a synthetically produced antibiotic, and as of the time of the filing of this application no biosynthetic pathway for the production of trimethoprim was known in the prior art. With regard to claim 9 in particular, DHFR2 encodes dihydrofolate reductase 2, and was a known trimethoprim resistance gene, as taught, for example, by Brisson and Hohn (see GenBank Accession K02118, comments section). The prior art does not teach that DHFR2 is involved in any biosynthetic pathway for trimethoprim. The prior art does not provide any examples of any organisms that naturally product trimethoprim.

The prior art provides methods for cloning genes and gene families from complex nucleic acid samples, see for example Compton *et al.* who teach degenerate amplification of gene

families, and Denoya (US 5728561), who exemplifies the cloning of an entire cluster of genes from S. avermitilis (Col. 9-10), and Rovnak *et al.*, cited in the art rejections herein.

Direction Provided and Working Examples

The specification teaches that trimethoprim (referred to therein as TMP) is a synthesized antibiotic, and that a search for a natural producer using genetic determinants is novel (p. 34, lines 16-17). The specification further suggests that the DHFR2 oligo targets a unique form of the DHFR protein that is unrelated to other forms of DHFR that confer clinical resistance to TMP, and based on this fact the specification speculates that DHFR2 may originate from a "TMP-like" pathway, and, following this logic should be clustered within the entire TMP-like pathway (p. 34, lines 18-23). However, beyond these assertions the specification does not provide any guidance as to what kinds of enzymes these additional genes encode. Their existence is speculative. That they can be isolated is entirely speculative, unsupported by any evidence or examples in the specification. The specification does not teach any organism that produces trimethoprim, nor does the specification teach how the whether or not the putative "TMP-like" pathway exists, and if it does exist whether or not it actually results in the production of trimethoprim.

The specification only teaches that DHFR2 has been used in the successful discovery of additional genes that confer resistance to trimethoprim and other folate antimetabolites (p. 35, lines 11-12), but does not exemplify the use of DHFR2 for the isolation of "trimethoprim coding genes."

Level of Skill in the Art and Level of Unpredictability

The level of skill in the art is high, but the unpredictability with regard to the practice of the claimed invention is higher since the existence of the genes targeted in the instant assay is entirely unknown. That is, it is unknown and unpredictable as to whether or not any biosynthetic pathway exists for the production of trimethoprim, an antibiotic which has heretofore been chemically synthesized. It is therefore highly unpredictable, for example, in claims 7 and 8 what the appropriate target genes for amplification are, and thus the production of appropriate primers to the target sequence is highly unpredictable. Furthermore, even with regard to claim 9, which states the primers should target the DHFR2 gene, that such primers would result in the amplification of genes that are "trimethoprim coding genes" is entirely unpredictable, given the absence of any evidence in the specification or the prior art that such genes or gene pathways containing such genes exist.

Quantity of Experimentation

The quantity of experimentation necessary to practice the claimed invention is extremely high. One would first have to confirm or in fact discover that a trimethoprim production pathway exists in any of the hundreds of millions of possible organisms on the earth. Then, even having made such a determination, one would have to undertake extensive gene cloning efforts to identify and clone from within the genome of the putative organism the genes which result in trimethoprim production, a project that would be complicated by the high degree of unpredictability with regard to the production of the antibiotic.

Conclusion

Thus, given the nature of the invention, the breadth of the claims, the minimal guidance in the prior art, the lack of working examples, the high degree of unpredictability and the high

quantity of experimentation necessary to practice the claimed invention, it is concluded that undue experimentation would be necessary to practice the claimed invention.

Conclusion

10. All elected claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C Switzer
Examiner
Art Unit 1634

September 4, 2003